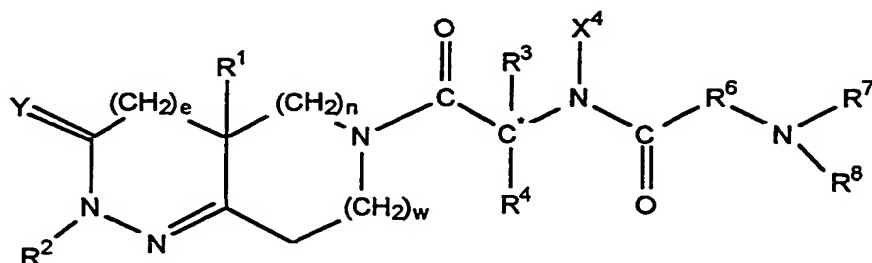


PRODUCT CLAIMS

What is claimed is:

1. A method for treating insulin resistance in a mammal, which comprises administering to said mammal an effective amount of a compound of formula I



I

- or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers, or the pharmaceutically acceptable salts and prodrugs thereof,
- wherein

- e is 0 or 1;
- n and w are each independently 0, 1 or 2;
- provided that w and n cannot both be 0 at the same time;
- Y is oxygen or sulfur;
- R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶, -(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶, -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹, -(C₁-C₁₀)alkyl, -(CH₂)_t-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl, -(CH₂)_q-Y¹-(CH₂)_t-A¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;
- where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6-$,
 $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

5 said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4) alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl, $-CO_2(C_1-C_4)$ alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4) alkyl;

R^2 is hydrogen, (C_1-C_8) alkyl, $-(C_0-C_3)$ alkyl- (C_3-C_8) cycloalkyl, $-(C_1-C_4)$ alkyl- A^1 or A^1 ;

10 where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;

R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl,

$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl, $-(C_1-C_5)$ alkyl- X^1 - (C_0-C_5) alkyl- A^1 or

15 $-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl- (C_3-C_7) cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with

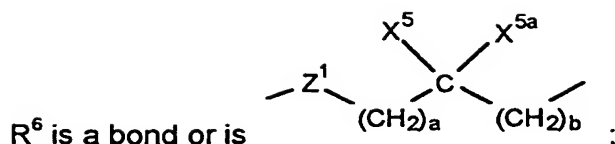
$-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,

$-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

20 R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially
25 saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom
30 to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;

5 the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

10 or the carbon bearing X⁵ or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R⁷ and R⁸ wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X⁵ or X^{5a} but not both may be on the carbon atom and R⁷ or R⁸ but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X⁵ and X^{5a} cannot be on the carbon atom and R⁷ and R⁸ cannot be on the nitrogen atom;

15 or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

20 or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

25 Z¹ is a bond, O or N-X², provided that when a and b are both 0 then Z¹ is not N-X² or O;

30

R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;
where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is
optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl,
-S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C₁-
5 C₁₀)alkyl or 1 to 3 (C₁-C₆)alkoxy; or

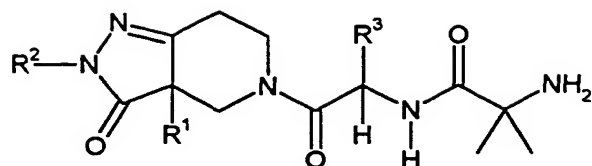
R⁷ and R⁸ can be taken together to form -(CH₂)_r-L-(CH₂)_r;
where L is C(X²)(X²), S(O)_m or N(X²);

A¹ for each occurrence is independently (C₅-C₇)cycloalkenyl, phenyl or a partially
saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally
10 having 1 to 4 heteroatoms independently selected from the group consisting of
oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially
saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally
having 1 to 4 heteroatoms independently selected from the group consisting of
nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully
15 unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms
independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or
optionally both rings if A¹ is a bicyclic ring system, with up to three
substituents, each substituent independently selected from the group
20 consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶,
-C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,
-S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy,
halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),
-N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,
25 -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and
tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy
then it can only be substituted with one methylenedioxy;

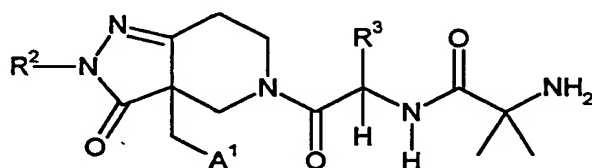
where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;
the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is
30 optionally independently substituted with phenyl, phenoxy,
(C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens,
1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-
C₆)alkoxy;

- X^{12} is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;
5 or X^{11} and X^{12} are taken together to form $-(CH_2)_rL^1-(CH_2)_r$;
where L^1 is $C(X^2)(X^2)$, O, S(O)_m or N(X^2);
r for each occurrence is independently 1, 2 or 3;
 X^2 for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted
10 (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^2 are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;
 X^3 for each occurrence is independently hydrogen or (C₁-C₆)alkyl;
 X^6 is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or
15 when there are two X^6 groups on one atom and both X^6 are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;
 X^7 is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and
25 m for each occurrence is independently 0, 1 or 2;
with the proviso that:
 X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²; and
when R⁶ is a bond then L is N(X^2) and each r in the definition $-(CH_2)_rL-(CH_2)_r$ is
30 independently 2 or 3.
2. A method according to claim 1 wherein said compound of formula I is of the following formula



or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers, or the pharmaceutically acceptable salts and prodrugs thereof where

- 5 R¹ is -CH₂-phenyl, R² is methyl and R³ is -(CH₂)₃-phenyl;
 R¹ is -CH₂-phenyl, R² is methyl and R³ is 3-indolyl-CH₂-;
 R¹ is -CH₂-phenyl, R² is ethyl and R³ is 3-indolyl-CH₂-;
 R¹ is -CH₂-4-fluoro-phenyl, R² is methyl and R³ is 3-indolyl-CH₂-;
 R¹ is -CH₂-phenyl, R² is methyl and R³ is -CH₂-O-CH₂-phenyl;
 10 R¹ is -CH₂-phenyl, R² is ethyl and R³ is -CH₂-O-CH₂-phenyl;
 R¹ is -CH₂-phenyl, R² is -CH₂CF₃ and R³ is -CH₂-O-CH₂-phenyl;
 R¹ is -CH₂-4-fluoro-phenyl, R² is methyl and R³ is -CH₂-O-CH₂-phenyl;
 R¹ is -CH₂-phenyl, R² is t-butyl and R³ is -CH₂-O-CH₂-phenyl; or
 R¹ is -CH₂-phenyl, R² is methyl and R³ is -CH₂-O-CH₂-3,4-di-fluoro-phenyl.
 15 3. A method according to claim 1 wherein said compound of formula I
 is of the formula



- or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the
 20 pharmaceutically acceptable salts and prodrugs thereof where
 R² is methyl; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-phenyl;
 R² is CH₂CF₃; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-3-chloro-phenyl;
 R² is CH₂CF₃; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-4-chloro-phenyl;
 R² is CH₂CF₃; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-2,4-di-chloro-phenyl;
 25 R² is CH₂CF₃; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-3-chloro-thiophene or
 R² is CH₂CF₃; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-2,4-di-fluoro-phenyl.

4. A method according to claim 1 wherein said compound of formula I or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof is the 3a(R,S),1(R) diastereomeric mixture, the 3a(R),1(R) diastereomer or the 3a(S),1(R) diastereomer of a compound selected from the group consisting of
- 2-amino-N-[1-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-butyl]-isobutyramide,
- 2-amino-N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[2-(3a-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[2-[3a-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[2-(3a-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[2-[3a-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-benzyloxymethyl-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[1-benzyloxymethyl-2-[3a-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl]-isobutyramide,
- 2-amino-N-[2-(3a-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-isobutyramide and
- 2-amino-N-[2-(3a-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

5. A method according to claim 4 wherein said compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartaric acid salt.

6. A method according to claim 1 wherein said compound of formula I or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof is the 3a-(R,S),1-(R)

diastereomeric mixture, the 3a-(R),1-(R) enantiomer or 3a-(S),1-(R) enantiomer of a compound selected from the group consisting of

2-amino-N-[1-benzyloxymethyl-2-(2-methyl-3-oxo-3a-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide;

2-amino-N-{1-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide;

2-amino-N-{1-(4-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide;

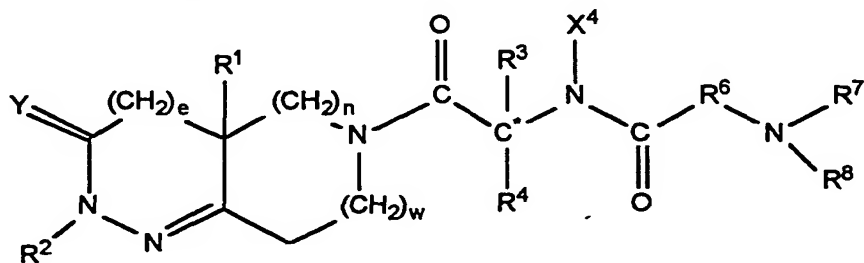
2-amino-N-{1-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide;

2-amino-N-{1-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide; and

2-amino-N-{1-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

7. A method for treating insulin resistance in a mammal according to claim 1 which additionally comprises administering to a mammal in need thereof a growth hormone releasing hormone or a functional analog thereof.

8. A pharmaceutical composition useful for treating insulin resistance in a mammal which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I



or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

5 e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹,

10 -(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹,
 -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹,
 -(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶,
 -(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶),
 -(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶,
 15 -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹,
 -(C₁-C₁₀)alkyl, -(CH₂)_t-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl,
 -(CH₂)_q-Y¹-(CH₂)_t-A¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

20 -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,
 -C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

25 t is 0, 1, 2 or 3;

said (CH₂)_q group and (CH₂)_t group may each be optionally substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl,
 -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C₁-C₄)alkyl;

30 R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹;

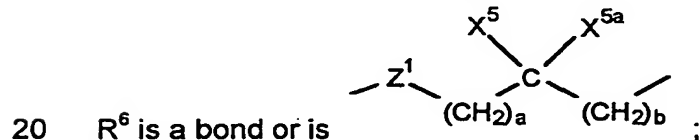
where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶),
 -S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 halogen;

R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl, $-(C_1-C_5)$ alkyl- X^1 -(C_1-C_5)alkyl, $-(C_1-C_5)$ alkyl- X^1 -(C_0-C_5)alkyl- A^1 or $-(C_1-C_5)$ alkyl- X^1 -(C_1-C_5)alkyl- (C_3-C_7) cycloalkyl;

5 where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ; X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, $(C_5-$
10 $C_7)$ cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4
15 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

25 the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1 , OX^2 , $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1
30 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both

- may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;
- 5 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;
- 10 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms
- 15 independently selected from the group consisting of nitrogen, sulfur and oxygen;
- Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;
- R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6) alkyl;
- 20 where the optionally substituted (C_1-C_6) alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or
- R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r$;
- 25 where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;
- A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially
- 30 saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully

unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

5 A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶,
 -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,
 -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy,
 10 halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),
 -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,
 -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and
 tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy
 then it can only be substituted with one methylenedioxy;

15 where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;
 the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is
 optionally independently substituted with phenyl, phenoxy,
 (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens,
 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-
 C₆)alkoxy;

20 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or
 thienyl, provided that when X¹² is not hydrogen, X¹² is optionally
 substituted with one to three substituents independently selected
 from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;
 or X¹¹ and X¹² are taken together to form -(CH₂)_rL¹-(CH₂)_r;

25 where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

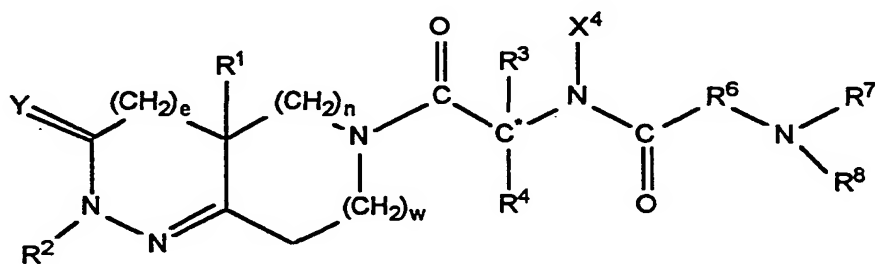
X² for each occurrence is independently hydrogen, optionally substituted (C₁-
 C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted
 (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are
 30 optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5
 halogens or 1-3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X^6 is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or when there are two X^6 groups on one atom and both X^6 are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X^7 is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and m for each occurrence is independently 0, 1 or 2; with the proviso that: X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O) X^6 , C(O) X^{12} , SO₂ X^6 or SO₂ X^{12} ; and when R⁶ is a bond then L is N(X²) and each r in the definition -(CH₂)_r-L-(CH₂)_r is independently 2 or 3.

9. A method for increasing levels of endogenous growth hormone, which comprises administering to a human or other animal in need thereof effective amounts of a functional somatostatin antagonist and a compound of formula I



or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof, wherein e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_t-A¹,

- 5 -(CH₂)_qN(X⁶)SO₂(CH₂)_t-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_t-A¹,
 -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_t-A¹,
 -(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_t-A¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶,
 -(CH₂)_qOC(O)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_t-A¹, -(CH₂)_qOC(O)N(X⁶)(X⁶),
 -(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_t-A¹, -(CH₂)_qN(X⁶)C(O)OX⁶,
 10 -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_t-A¹,
 -(C₁-C₁₀)alkyl, -(CH₂)_t-A¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl,
 -(CH₂)_q-Y¹-(CH₂)_t-A¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

- 15 -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,
 -C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

- 20 t is 0, 1, 2 or 3;

said (CH₂)_q group and (CH₂)_t group may each be optionally substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl,
 -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C₁-C₄)alkyl;

- 25 R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹;

where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶),
 -S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 halogen;

R³ is A¹, (C₁-C₁₀)alkyl, -(C₁-C₆)alkyl-A¹, -(C₁-C₆)alkyl-(C₃-C₇)cycloalkyl,

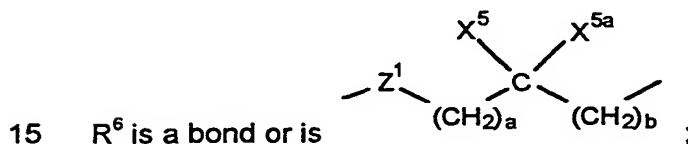
- 30 -(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl, -(C₁-C₅)alkyl-X¹-(C₀-C₅)alkyl-A¹ or
 -(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl-(C₃-C₇)cycloalkyl;

where the alkyl groups in the definition of R³ are optionally substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX³;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,
 $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1 , OX^2 , $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered

ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

5 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms
10 independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6) alkyl;

15 where the optionally substituted (C_1-C_6) alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

20 where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially
25 saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

30 A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$,

-C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,
 -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy,
 halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),
 -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,
 -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and
 tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy
 then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is
 optionally independently substituted with phenyl, phenoxy,
 (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens,
 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-
 C₆)alkoxy;

X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or
 thienyl, provided that when X¹² is not hydrogen, X¹² is optionally
 substituted with one to three substituents independently selected
 from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_rL¹-(CH₂)_r;

where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-
 C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted
 (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are
 optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5
 halogens or 1-3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X⁶ is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-
 C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-
 halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally
 substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently
 substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -
 S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6) alkyl, the two (C_1-C_6) alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

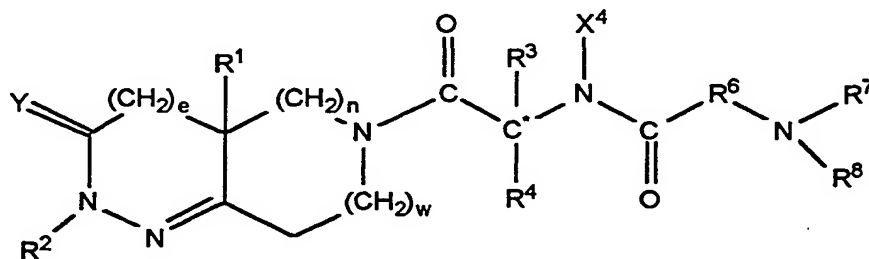
- 5 X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and
m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

- 10 when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_rL-(CH_2)_r$ is independently 2 or 3.

10. A method of treating or preventing congestive heart failure, obesity or frailty associated with aging, which comprises administering to a mammal in need thereof effective amounts of a functional somatostatin antagonist and a
15 compound of formula I



I

- or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the
20 pharmaceutically acceptable salts and prodrugs thereof,
wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

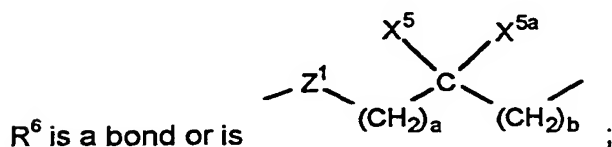
- 25 Y is oxygen or sulfur;

R^1 is hydrogen, $-CN$, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_rA^1$,
 $-(CH_2)_qN(X^6)SO_2(CH_2)_rA^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_rA^1$,
 $-(CH_2)_qN(X^6)C(O)N(X^6)X^6$, $-(CH_2)_qC(O)N(X^6)X^6$, $-(CH_2)_qC(O)N(X^6)(CH_2)_rA^1$,

- $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_tA^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$,
 $-(CH_2)_qOC(O)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,
 $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_tA^1$, $-(CH_2)_qN(X^6)C(O)OX^6$,
 $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_tA^1$,
5 $-(C_1-C_{10})alkyl$, $-(CH_2)_tA^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$,
 $-(CH_2)_q-Y^1-(CH_2)_tA^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;
where the alkyl and cycloalkyl groups in the definition of R^1 are optionally
substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$,
 $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl or 1, 2 or 3
10 fluoro;
 Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6$,
 $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;
q is 0, 1, 2, 3 or 4;
t is 0, 1, 2 or 3;
15 said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with
hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$,
 $-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 $(C_1-$
 $C_4)alkyl$;
 R^2 is hydrogen, $(C_1-C_8)alkyl$, $-(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkyl-A^1$ or A^1 ;
20 where the alkyl groups and the cycloalkyl groups in the definition of R^2 are
optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$,
 $-S(O)_m(C_1-C_6)alkyl$, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;
 R^3 is A^1 , $(C_1-C_{10})alkyl$, $-(C_1-C_6)alkyl-A^1$, $-(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl$,
 $-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl$, $-(C_1-C_5)alkyl-X^1-(C_0-C_5)alkyl-A^1$ or
25 $-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl-(C_3-C_7)cycloalkyl$;
where the alkyl groups in the definition of R^3 are optionally substituted with
 $-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;
 X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,
 $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;
30 R^4 is hydrogen, $(C_1-C_6)alkyl$ or $(C_3-C_7)cycloalkyl$, or R^4 is taken together with R^3
and the carbon atom to which they are attached and form $(C_5-C_7)cycloalkyl$, $(C_5-$
 $C_7)cycloalkenyl$, a partially saturated or fully saturated 4- to 8-membered ring
having 1 to 4 heteroatoms independently selected from the group consisting of

oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1 , OX^2 , $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2

heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6) alkyl;

where the optionally substituted (C_1-C_6) alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_rL-(CH_2)_r$;

where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6) alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$ alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$ -phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$,

$-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6) alkyl;

5 the optionally substituted (C_1-C_6) alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6) alkoxycarbonyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10}) alkanoyloxy or 1 to 3 (C_1-C_6) alkoxy;

10 X^{12} is hydrogen, (C_1-C_6) alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3 , OCH_3 , OCF_3 and CF_3 ;

or X^{11} and X^{12} are taken together to form $-(CH_2)_rL^1-(CH_2)_r$;

15 where L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_3-C_7) cycloalkyl, where the optionally substituted (C_1-C_6) alkyl and optionally substituted (C_3-C_7) cycloalkyl in the definition of X^2 are
20 optionally independently substituted with $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1-3 OX^3 ;

X^3 for each occurrence is independently hydrogen or (C_1-C_6) alkyl;

X^6 is independently hydrogen, optionally substituted (C_1-C_6) alkyl, (C_2-C_6) halogenated alkyl, optionally substituted (C_3-C_7) cycloalkyl, (C_3-C_7) -
25 halogenatedcycloalkyl, where optionally substituted (C_1-C_6) alkyl and optionally substituted (C_3-C_7) cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4) alkyl, hydroxyl, (C_1-C_4) alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl, carboxylate (C_1-C_4) alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6) alkyl, the two (C_1-C_6) alkyl groups may be optionally joined and, together with
30 the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

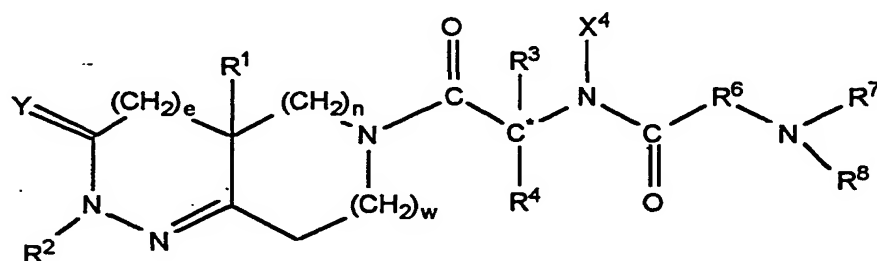
- 5 when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_rL-(CH_2)_r$ is independently 2 or 3.

11. A method according to claim 10 wherein said functional somatostatin antagonist is an alpha-2 adrenergic agonist.

12. A method according to claim 11 wherein said alpha-2 adrenergic
10 agonist is selected from the group consisting of clonidine, xylazine and medetomidine.

13. A method according to claim 12 wherein said compound of formula I
is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-
[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartaric acid
15 salt.

14. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier, an amount of an alpha-2 adrenergic agonist and an amount of a compound of formula I



20

or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers or the pharmaceutically acceptable salts and prodrugs thereof, wherein

25 e is 0 or 1;

n and w are each independently 0, 1 or 2;

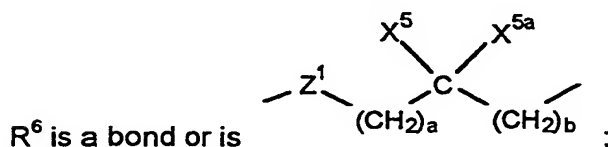
provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

- R^1 is hydrogen, $-\text{CN}$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{X}^6$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})(\text{CH}_2)_t\text{A}^1$,
 $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{SO}_2(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{SO}_2\text{X}^6$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_t\text{A}^1$,
 $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_t\text{A}^1$,
 $-(\text{CH}_2)_q\text{C}(\text{O})\text{OX}^6$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{O}(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{OX}^6$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{X}^6$,
5 $-(\text{CH}_2)_q\text{OC}(\text{O})(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$,
 $-(\text{CH}_2)_q\text{C}(\text{O})\text{X}^6$, $-(\text{CH}_2)_q\text{C}(\text{O})(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{OX}^6$,
 $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{SO}_2\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{S}(\text{O})_m\text{X}^6$, $-(\text{CH}_2)_q\text{S}(\text{O})_m(\text{CH}_2)_t\text{A}^1$,
 $-(\text{C}_1\text{-C}_{10})\text{alkyl}$, $-(\text{CH}_2)_t\text{A}^1$, $-(\text{CH}_2)_q\text{-(C}_3\text{-C}_7\text{)cycloalkyl}$, $-(\text{CH}_2)_q\text{-Y}^1\text{-(C}_1\text{-C}_6\text{)alkyl}$,
 $-(\text{CH}_2)_q\text{-Y}^1\text{-(CH}_2)_t\text{A}^1$ or $-(\text{CH}_2)_q\text{-Y}^1\text{-(CH}_2)_t\text{-(C}_3\text{-C}_7\text{)cycloalkyl}$;
10 where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(\text{C}_1\text{-C}_4)\text{alkyl}$, hydroxyl, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, carboxyl, $-\text{CONH}_2$,
 $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{CO}_2(\text{C}_1\text{-C}_4)\text{alkyl ester}$, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;
 Y^1 is O, $\text{S}(\text{O})_m$, $-\text{C}(\text{O})\text{NX}^6$ -, $-\text{CH}=\text{CH}$ -, $-\text{C}\equiv\text{C}$ -, $-\text{N}(\text{X}^6)\text{C}(\text{O})$ -, $-\text{C}(\text{O})\text{NX}^6$ -,
15 $-\text{C}(\text{O})\text{O}$ -, $-\text{OC}(\text{O})\text{N}(\text{X}^6)$ - or $-\text{OC}(\text{O})$ -;
 q is 0, 1, 2, 3 or 4;
 t is 0, 1, 2 or 3;
said $(\text{CH}_2)_q$ group and $(\text{CH}_2)_t$ group may each be optionally substituted with
hydroxyl, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, carboxyl, $-\text{CONH}_2$, $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_6)\text{alkyl}$,
20 $-\text{CO}_2(\text{C}_1\text{-C}_4)\text{alkyl ester}$, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 $(\text{C}_1\text{-C}_4)\text{alkyl}$;
 R^2 is hydrogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $-(\text{C}_0\text{-C}_3)\text{alkyl-(C}_3\text{-C}_8\text{)cycloalkyl}$, $-(\text{C}_1\text{-C}_4)\text{alkyl-A}^1$ or A^1 ;
where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-\text{C}(\text{O})\text{OX}^6$, $-\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{N}(\text{X}^6)(\text{X}^6)$,
25 $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{A}^1$, $-\text{C}(\text{O})(\text{X}^6)$, CF_3 , CN or 1, 2 or 3 halogen;
 R^3 is A^1 , $(\text{C}_1\text{-C}_{10})\text{alkyl}$, $-(\text{C}_1\text{-C}_6)\text{alkyl-A}^1$, $-(\text{C}_1\text{-C}_6)\text{alkyl-(C}_3\text{-C}_7\text{)cycloalkyl}$,
 $-(\text{C}_1\text{-C}_5)\text{alkyl-X}^1\text{-(C}_1\text{-C}_5\text{)alkyl}$, $-(\text{C}_1\text{-C}_5)\text{alkyl-X}^1\text{-(C}_0\text{-C}_5\text{)alkyl-A}^1$ or
 $-(\text{C}_1\text{-C}_5)\text{alkyl-X}^1\text{-(C}_1\text{-C}_5\text{)alkyl-(C}_3\text{-C}_7\text{)cycloalkyl}$;
where the alkyl groups in the definition of R^3 are optionally substituted with
30 $-\text{S}(\text{O})_m(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{OX}^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;
 X^1 is O, $\text{S}(\text{O})_m$, $-\text{N}(\text{X}^2)\text{C}(\text{O})$ -, $-\text{C}(\text{O})\text{N}(\text{X}^2)$ -, $-\text{OC}(\text{O})$ -, $-\text{C}(\text{O})\text{O}$ -, $-\text{CX}^2=\text{CX}^2$ -,
 $-\text{N}(\text{X}^2)\text{C}(\text{O})\text{O}$ -, $-\text{OC}(\text{O})\text{N}(\text{X}^2)$ - or $-\text{C}\equiv\text{C}$ -;

R⁴ is hydrogen, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl, or R⁴ is taken together with R³ and the carbon atom to which they are attached and form (C₅-C₇)cycloalkyl, (C₅-C₇)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

- 10 X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

- 15 X⁵ and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;
the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);
- 20

or the carbon bearing X⁵ or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R⁷ and R⁸ wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X⁵ or X^{5a} but not both may be on the carbon atom and R⁷ or R⁸ but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X⁵ and X^{5a} cannot be on the carbon atom and R⁷ and R⁸ cannot be on the nitrogen atom;

- 25 or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having
- 30

- 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;
or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;
- Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;
- R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6) alkyl; where the optionally substituted (C_1-C_6) alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or
- R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r$; where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;
- A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;
- A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6) alkyl, nitro, cyano, benzyl,

5 -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶), -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

10 the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

15 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_rL¹-(CH₂)_r;

where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

20 X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

25 X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

30 X⁶ is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X⁶ groups on one atom and both X⁶ are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with

the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and m for each occurrence is independently 0, 1 or 2;

5 with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

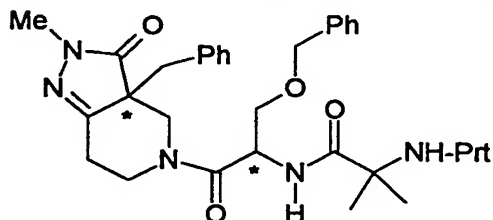
when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_rL-(CH_2)_r-$ is independently 2 or 3.

10 15. A method according to claim 1 wherein the condition associated with insulin resistance is type I diabetes, type II diabetes, hyperglycemia, impaired glucose tolerance or an insulin resistant syndrome or state.

16. A method according to claim 1 wherein the condition associated with insulin resistance is associated with obesity or old age.

15 17. A method of treating insulin resistance in a mammal which comprises administering to a mammal in need thereof an effective amount of a growth hormone releasing peptide or a growth hormone releasing peptide mimetic or a pharmaceutically acceptable salt thereof.

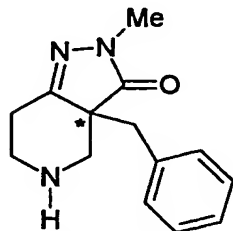
18. A process for the preparation of the compound of formula k,



20

(k)

, which comprises reacting the compound of

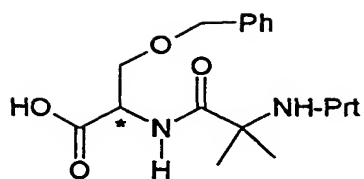


Free Base

(g)

formula g,

, with the compound of formula j,

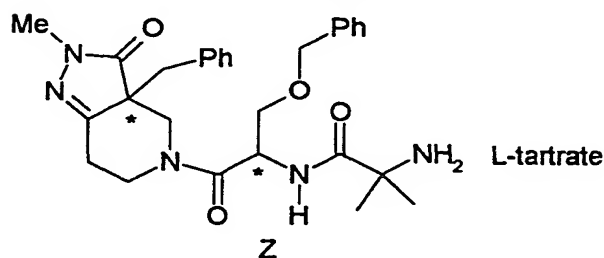


(i)

, where Prt is an amine protecting group, in the presence of an organic base, a peptide coupling reagent, and a reaction inert solvent at a temperature between about -78 °C to about -20 °C to yield the compound of formula k.

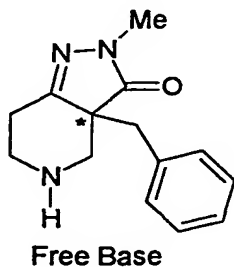
- 5 19. A process according to claim 18 where the peptide coupling reagent is 1-propane phosphonic acid cyclic anhydride and the compound of formula g has the R-configuration, the compound of formula j has the R-configuration and the compound of formula k has the 3a-(R),1-(R) configuration.

20. A process for the preparation of the compound of formula Z,



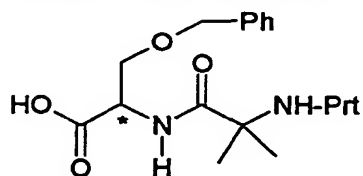
10

, which comprises reacting the



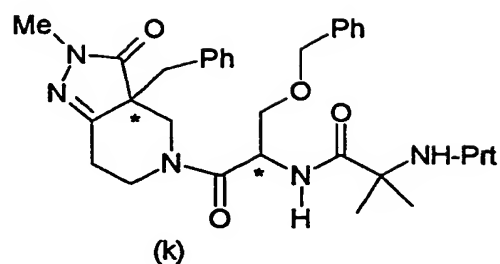
compound of formula g,

, with the compound of formula j,



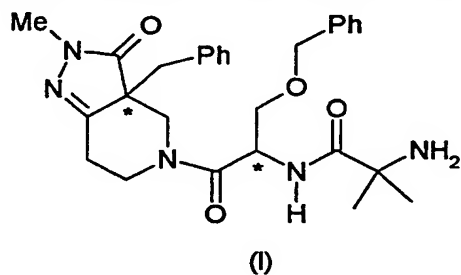
(i)

, in the presence of an organic base, a peptide coupling reagent, and a reaction inert solvent at a temperature between about -78 °C to about



-20 °C to yield the compound of formula k,

deprotecting the compound of formula k to yield the compound of formula l,

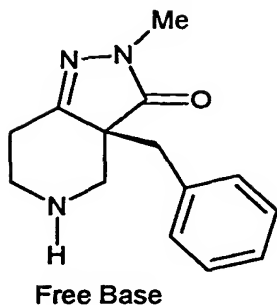


; reacting the compound of formula l with L-

tartaric acid in an alcoholic solvent to yield the compound of formula Z.

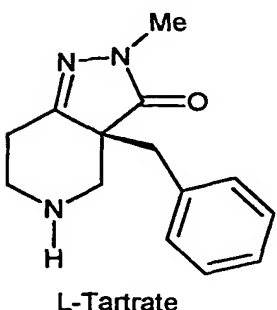
- 5 21. A process according to claim 20 where the peptide coupling reagent is 1-propane phosphonic acid cyclic anhydride and the compound of formula g has the R-configuration, the compound of formula j has the R-configuration and each of the compounds of formula k, l and Z has the 3a-(R), 1-(R) configuration.

22. A process for the preparation of the compound of formula g,



(g)

, which comprises reacting the compound of formula f,

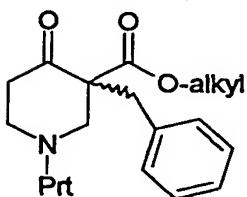


(f)

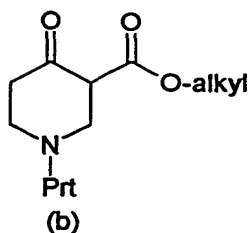
, with a base in an inert solvent at a temperature of about -50 to -10 °C wherein the chirality of the benzyl group is maintained, to yield the compound of formula g.

5

23. A process for the preparation of the compound of formula c,



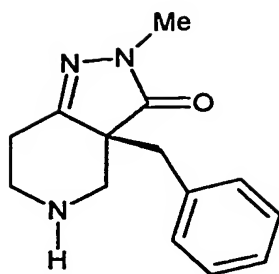
, which comprises reacting the compound of formula b,



, where Prt is an amine protecting group, with an inorganic or organic base and benzyl bromide in a reaction inert solvent to yield the compound of formula c.

10

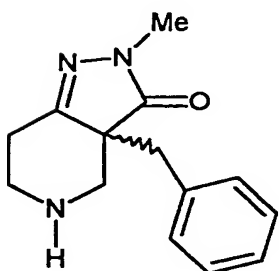
24. A process for the preparation of the compound of formula f,



L-Tartrate

(f)

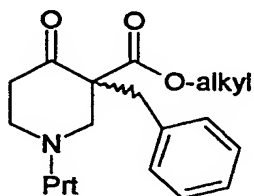
, which comprises reacting the compound of formula e,



(e)

, with L-tartaric acid in a reaction inert organic solvent.

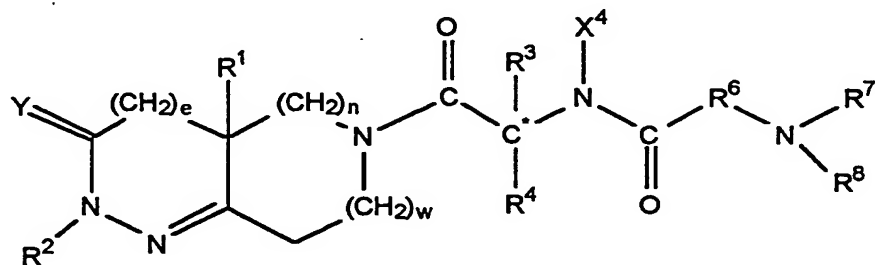
25. The R,S-enantiomeric mixture, the R-enantiomer or the S-enantiomer of the compound of formula



5

, where Prt is hydrogen or an amine protecting group.

26. A method of treating sleep disorders in a mammal suffering from sleep disorders comprising administering to said mammal an effective amount of a compound of formula I



10

I

or the stereoisomeric mixtures, diastereomerically enriched, diastereomerically pure, enantiomerically enriched or enantiomerically pure isomers, or the pharmaceutically acceptable salts and prodrugs thereof,

wherein

5 e is 0 or 1;

n and w are each independently 0, 1 or 2;

provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_tA¹,

10 -(CH₂)_qN(X⁶)SO₂(CH₂)_tA¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_tA¹,

-(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_tA¹,

-(CH₂)_qC(O)OX⁶, -(CH₂)_qC(O)O(CH₂)_tA¹, -(CH₂)_qOX⁶, -(CH₂)_qOC(O)X⁶,

-(CH₂)_qOC(O)(CH₂)_tA¹, -(CH₂)_qOC(O)N(X⁶)(CH₂)_tA¹, -(CH₂)_qOC(O)N(X⁶)(X⁶),

-(CH₂)_qC(O)X⁶, -(CH₂)_qC(O)(CH₂)_tA¹, -(CH₂)_qN(X⁶)C(O)OX⁶,

15 -(CH₂)_qN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)_qS(O)_mX⁶, -(CH₂)_qS(O)_m(CH₂)_tA¹,

-(C₁-C₁₀)alkyl, -(CH₂)_tA¹, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_q-Y¹-(C₁-C₆)alkyl,

-(CH₂)_q-Y¹-(CH₂)_tA¹ or -(CH₂)_q-Y¹-(CH₂)_t-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

20 -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,

-C(O)O-, -OC(O)N(X⁶)- or -OC(O)-;

q is 0, 1, 2, 3 or 4;

25 t is 0, 1, 2 or 3;

said (CH₂)_q group and (CH₂)_t group may each be optionally substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂, -S(O)_m(C₁-C₆)alkyl,

-CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C₁-C₄)alkyl;

30 R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹;

where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶),

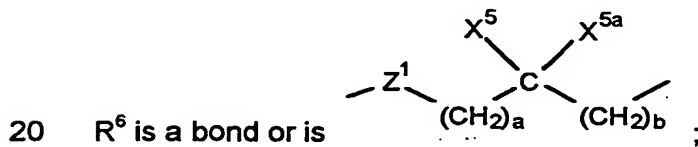
-S(O)_m(C₁-C₆)alkyl, -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1, 2 or 3 halogen;

R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl, $-(C_1-C_5)$ alkyl- X^1 -(C_1-C_5)alkyl, $-(C_1-C_5)$ alkyl- X^1 -(C_0-C_5)alkyl- A^1 or $-(C_1-C_5)$ alkyl- X^1 -(C_1-C_5)alkyl- (C_3-C_7) cycloalkyl;

5 where the alkyl groups in the definition of R^3 are optionally substituted with $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ; X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$, $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

25 the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1 , OX^2 , $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

30 or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both

may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

5 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

10 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms
15 independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6) alkyl;

20 where the optionally substituted (C_1-C_6) alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_rL-(CH_2)_r$;

25 where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially
30 saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully

unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three
 5 substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶, -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl, -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),
 10 -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;
 15 the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

20 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃; or X¹¹ and X¹² are taken together to form -(CH₂)_rL¹-(CH₂)_r;

25 where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are
 30 optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1-3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

- X^6 is independently hydrogen, optionally substituted (C_1-C_6) alkyl, (C_2-C_6) halogenated alkyl, optionally substituted (C_3-C_7) cycloalkyl, (C_3-C_7) -halogenatedcycloalkyl, where optionally substituted (C_1-C_6) alkyl and optionally substituted (C_3-C_7) cycloalkyl in the definition of X^6 is optionally independently substituted by 1 or 2 (C_1-C_4) alkyl, hydroxyl, (C_1-C_4) alkoxy, carboxyl, $CONH_2$, - $S(O)_m(C_1-C_6)$ alkyl, carboxylate (C_1-C_4) alkyl ester, or 1H-tetrazol-5-yl; or
- 5 when there are two X^6 groups on one atom and both X^6 are independently (C_1-C_6) alkyl, the two (C_1-C_6) alkyl groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring
- 10 optionally having oxygen, sulfur or NX^7 ;
- X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and
- m for each occurrence is independently 0, 1 or 2;
- with the proviso that:
- X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form
- 15 $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and
- when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_rL-(CH_2)_r$ is independently 2 or 3.